FETAL - MATERNAL HEMORRHAGE: A COMPARISON OF TWO CASES

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Almost all pregnancies have only a small amount of fetal blood in maternal circulation. In some rare cases, massive fetal-maternal hemorrhage can result in rapid fetal hemodynamic collapse, leading to severe fetal morbidity and mortality. Unfortunately, fetal – maternal hemorrhage is rarely diagnosed prenatally because clinical manifestations are often nonspecific, subtle, and difficult to identify at the time of the event. In this article, we present two cases of large fetal-maternal hemorrhage which were proven by the Kleihaure-Betke test to highlight the difference between nonspecific initial manifestations and the outcome of each case. Moreover, we would like to emphasize the importance of early detection and timely treatment to prevent potentially devastating complications of this condition.

Keywords: Fetal-maternal hemorrhage (FMH), neonatal anemia, Kleihaure-Betke (KB) test.

I. INTRODUCTION

Fetal – maternal hemorrhage (FMH) refers to the transfer of fetal blood into the maternal circulation that might happen at any stage of the pregnancy. Fortunately, the volume lost is typically small, with less than 0.025 ml of fetal red cells observed in 75% of cases.[1] When in small volume, it is considered as a physiological event, whereas massive volume FMHs can cause devasting complications. It is difficult to diagnose FMH case because the majority present with nonspecific symptoms and, depending on the duration and severity.[2] Massive FMH often results in adverse pregnancy outcomes, including stillbirth, hypoxic-ischemic encephalopathy, premature, severe neonatal anemia, abnormal fetal heart rate tracings, hydrops, or decrease of fetus movements. The diagnosis is made by performing a Kleihauer – Betke test on maternal blood, which allows measurement of the amount of fetal hemoglobin transferred from a fetus to its mother's bloodstream. In addition, FMH can also be confirmed by flow cytometry, using anti-fetal hemoglobin antibodies (anti-HbF). Early identification of FMH is essential. Most cases of massive FMH are diagnosed only in the neonatal period of present fetal death.[1,3]

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II. CASE PRESENTATION

1. Case 1

A 2900g female infant was born to a 39-year-old G3P3 mother at 39 weeks of gestation without a history of trauma, infection, or vaginal bleeding. The pregnancy had been asymptomatic until one month before delivery when decreased fetal movements were noted by the mother occasionally and she was evaluated at a private clinic. No abnormality was detected by ultrasound until 5 days before admission. The mother complained of malaise, diarrhea, mild abdominal pain, with no edema.

The infant was delivered via vaginal delivery in 20 minutes. The baby had a pale appearance and hypoxemia, leading to severe bradycardia. The baby immediately required aggressive resuscitation in the delivery room with intubation, positive pressure ventilation,

and chest compressions. Apgar scores were not provided by obstetricians. Then the infant was transferred to neonatal intensive care for further investigations.

On admission, her vital signs were relatively stable except for circulatory dysfunction. The peripheral blood pressure was unmeasurable and the heart rate was 100 bpm. Cold extremities, delayed capillary refill, and weak peripheral pulses indicated poor blood perfusion. A preliminary physical exam also revealed no signs of circulatory volume overload as the liver was impalpable. Subcutaneous edema and multi-membrane effusion were not detected. Immediately, volume resuscitation was started, followed by quickly placing umbilical catheters.

Initial arterial blood gas revealed uncompensated metabolic acidosis with pH 7.03, pCO_2 41 mm Hg, HCO3- 10,8mmol/lL, base excess -20 mmol/L, and lactate >15mmol/L. The hematocrit was under 15%, with unmeasurable hemoglobin. Our initial hypothesis was severe fetal anemia leading to birth asphyxia. Due to the empiric clinical diagnosis of this situation, cooling therapy was started 3 hours after birth as well as a red blood cell transfusion (15ml/kg). After blood transfusion, since the hematocrit continued to decrease to 6.7%, the infant experienced an urgent exchange blood transfusion. Biochemical markers were also suggestive of persistent hypoxic injury, such as LDH 2300 UI/L, lactate 16.7 mmol/L, coagulation disorders (**Table 1**), abnormal liver function test, and increased creatinine (**Table 2**).

Table 1. Coagulation profile

Test	Value	Normal range
Prothrombin Time	20.6 sec	9.9-12.4
Activated Partial Thromboplastin Time	39.7 sec	25.1-36.5
INR	1.88	1.05-1.35
Fibrinogen	1.53 g/L	1.43-4.02

Table 2. Liver and Kidney function test

Test	Value	Normal range
Alanine aminotransferase	47 U/L	6-50
Aspartate aminotransferase	199 U/L	30-146
Albumin	17.7 g/L	34-43
Total protein	28.3 g/L	41-63
Creatinine	115 umol/L	30-81
Urea	3.15 mmol/L	1.1-8

The next step was to determine the underlying reasons for this severe anemic condition. High reticulocyte counts of 25,5% suggested chronic anemia in utero. Both the mother's and the neonate's blood type was group A, RhD+, and the mother's antibody screen was negative. There was no visible bleeding or internal hemorrhage on abdominal/head ultrasonography. There

were no finding of congenital infections such as TORCH (toxoplasmosis, syphilis, rubella, cytomegalovirus, and herpes) infection from laboratory test. Other etiologies of these disorders were considered and prevented, including sepsis evaluation as well as empiric antibiotics. An echocardiogram at 1 day of age showed no abnormality apart from impaired cardiac contractile function (one of the consequences of persistent hypoxic) which required inotropic support with dobutamine and became normal after 3 days.

Eventually, a Kleihauer- Betke (KB) test performed on the mother's blood after delivery demonstrated 1.8% fetal red cells suggestive of 90 ml of fetal blood in the maternal circulation or 30ml/kg of fetal blood, confirming the significant amount of fetal-maternal hemorrhage.

After 3 hours of treatment, improvement was obtained by more stable hemodynamic condition and the post-transfusion hematocrit was 40%. Although the infant's blood gases initially showed metabolic acidosis for several hours, the pH eventually increased to 7.3 at 11 hours of age.

The infant was weaned from respiratory support and extubated at 36 hours of age. Physical symptoms of neurological problems were not detected. Cerebral spinal fluid analysis was also obtained and was later noted to be normal. On the 7th day of life, a magnetic resonance imaging (MRI) test indicated only slightly increased signal of the bilateral thalamus and hypothalamus. Finally, the infant was discharged home on the 13th day of life with no supplementation of oxygen for breathing, normal muscle tone, and good neonatal reflexes.

2. Case 2

A male infant was born to a thirty-four-year-old female G3P3 at 37 weeks of gestation. Abnormal signs of the pregnancy were unrecognizable except the fetal ascites confirmed by ultrasonography. An urgent cesarean section was performed due to the fetal heart rate deceleration. The infant was noted to be very pale and required aggressive resuscitation. Apgar score were 2, 3, and 5 at 1, 5, and 10 minutes, respectively. Birth weight was 2670g.

The infant was transferred to neonatal intensive care for further evaluation and management. Severe hypoxia and circulatory impairment were promptly recognized with severe anemia and unresponsive to mechanical ventilation with adequate oxygen levels, meaning that the underlying cause of this condition was the critical lack of erythrocytes, particularly hemoglobin which is a protein responsible of providing the oxygen for the cells. As a result, the infant underwent persistent metabolic acidosis with a pH of under 6.9, pCO2 23 mmHg, bicarbonate 5.3 mmol/L, base excess -25mmol/L, lactate 15 mmol/L, and hypotensive because of the hypoxic cardiac cell and insufficient circulatory volume. The fetal hemoglobin was 2.6 g/dL with high reticulocytes. The treatment consisted of cooling therapy and packed red blood cell transfusion. At the same time, laboratory tests were performed to identify the etiology and complications of anemia. The range of Glucose-6-phosphate dehydrogenase (G6PD) activity was normal, and there was no hemolytic of ABO and Rh incompatibility confirmed by negative- Coombs tests. There was no visible bleeding or internal hemorrhage on abdominal/head ultrasonography. The congenital viral infection was also excluded. Because of these findings, we suspected the underlying cause of this condition was the massive and chronic fetomaternal hemorrhage. Indeed, the KB test indicated 8.3% of fetal erythrocytes into the maternal bloodstream,

estimating approximately 415 ml of fetal blood. Chronic anemia were detected by further evaluation, including the hydrops fetalis of the infant with skin edema and ascites, and the evidence of congestive heart failures such as hepatomegaly and cardiomegaly.

However, the infant condition tended to deteriorate with the requirement of High-Frequency Oscillatory Ventilation and high doses of three inotropes (Dopamin, Dobutamine, and Adrenaline). The severe pulmonary hypertension and decreased ejection fraction were noted in the echocardiogram and the biochemical findings indicated severe liver and renal dysfunction. Fortunately, in the following days, after attempts at resuscitation and multiple blood transfusions, the blood gas increased to the normal limitations at 48 hours of age, and levels of hemoglobin gradually increased up to 13.8 g/dL on the 5th day of life. On the 10th day of life, further neurological examinations observed microbleeds in the bilateral frontal lobe and around the cerebral ventricles by MRI, and sharp waves in the center on electroencephalography. The infant was discharged to home with a hypertonic condition and no seizure.

III. DISCUSSION

Fetal maternal hemorrhage occurs when the fetal blood crosses the placenta barrier into the maternal bloodstream. This condition was first described by Wiener in 1948,[4] and was later confirmed as a cause of neonatal anemia by Chown in 1954.[5] FMH in small amounts occurs frequently, with less than 0.025 ml of fetal red cell present in 75% postpartum conditions, and it usually happens without any clinical manifestation and complication.[6] The cut-off volume for clinically significant FMH has been defined as > 30ml, and when this volume is up to 150ml, it could be defined as massive or severe FMH. Massive FHM occurs in approximately 0,3% of pregnancies,[7] which can lead to many significant complications in infants such as unexplained stillbirth, hydrops, abnormal fetal heart rate tracings, decrease of fetal movements, and neonatal anemia.[1]

On the other hand, more factors including the rate of blood loss, fetal size, and gestational age played essential roles in the severity of clinical manifestations. Indeed, a large cumulative blood loss caused by the persistence of intermittent FMH likely leads to various clinical extents of consequences including fetal anemia, heart failure, and hydrops fetalis over time. In detail, the adaption depends on the ability of fetal compensatory hemopoietic mechanisms. Besides, another important component of FMH prognosis is gestational age. Preterm infants in comparison with term infants have less stress tolerations and resistance to morbidities. The periods of pregnancy also affect the intravascular volume (calculated in mL/kg), which is mentioned earlier to clarify the percentage of blood loss versus total volume.[2]

So what are the causes of FMH? This is still a controversial debate topic that is continuously researched . There have been many studies about this issue reported recently. Those studies show that there are many etiologies that have been associated with FMH, but about 80% of these cases have no clear explanation.[1] Most FHM cases are idiopathic. However, FMH can be caused by iatrogenic or obstetrical complications. It may result from antepartum procedures (eg, amniocentesis, percutaneous umbilical blood sampling, intrauterine manipulation, caesarian section) or clinical complications (eg, abruptio placentae, placenta previa, and threatened abortion).[8] In our clinical reports, we could not identify the exact causes of severe FHM in both neonates, so we concluded that these cases were idiopathic.

Spontaneous massive FMH can occur at any time and increase throughout pregnancy: 4% in the first trimester, 12% in the second trimester, 45% in the third trimester, and 60% at delivery.[9] The initial symptoms of FMH are various, subtle, and nonspecific. There are three main clinical presentations described in the literature, including massive acute bleeding resulting in fetal demise, massive but non-lethal acute FMH or chronic intermittent FMH with the complications of nonimmune hydrops fetalis, unexplained profound anemia, and circulatory collapse. In two of our reported cases, both patients had severe anemia, respiratory distress syndrome, and hemodynamic dysfunction, which resulted in the requirement of immediate aggressive resuscitation at delivery time. Several cases have no predictable sign, even in laboratory investigations, if the fetus could sufficiently compensate for the blood loss. The predominance of pathological FMH cases reported are acute progression with uneventful obstetric history and decreased or absent fetal movement are the most popular presenting symptoms. FHM can manifest as sinusoidal pattern or fetal tachycardia (appropriately 10% of cases).[1]

When FMH is suspected, there are tests to identify fetal red blood cells in the mother's circulation. The KB test is the most frequent test used to confirm fetus's blood in the mother's bloodstream. This test was first described in 1957 by Kleihauer, Braun, and Betke.[10] It is based on the principle that the hemoglobin F, a dominant component of fetal red blood cells, is relatively resistant to acid elution when compared with the hemoglobins of adult red blood cells (hemoglobin A1 and A2).[1] There is a formula to calculate the amount of FMH based on the number of fetus red blood cells found. The formular of KB test is as folows:

Percentage of fetal cells = Number of fetal cells X 100 / Total number of Red blood cells

After calculating the percentage of fetal cells, we can calculate the volume of fetal blood loss in mother's bloodtream by the following formula:

Volume (mL) of fetal blood = Percentage of fetal cells x 50

However, KB test has numerous limitations, including low sensitivity, poor reproducibility, and a tendency to overestimate the volume of FMH.[10] In addition, there are some other tests that could be used to diagnose FMH. Flow cytometry, based on the use of anti-fetal hemoglobin for detection of fetal hemoglobin in fetal erythrocytes, represents an improvement of KB test because it is more specific and precise.[1]

According to estimation, neonatal anemia has been reported in 35% of cases.[11] In severe cases, signs of shock and circulatory failure are often present.[12] In this situation, prompt recognition and intervention are the most essential key. Exchange transfusion with whole blood may allow for rapid correction of the anemia, especially when there is normal or increased circulating blood volume, which could minimize the complications associated with hypervolemia, cardiac compromise and improve the neurological outcome.[1,13] Unless the clinical condition is unstable, the transfusion with the packed red cells may be preferred[14]. Additionally, a sepsis evaluation and empiric antibiotics are warranted. The other causes of unexpected anemia such as isoimmune hemolytic anemia (Rh incompatibility), or autoimmune causes, congenital infections could be considered alternative diagnoses, besides FMH.[15]

In our cases, the clinical presentations were suggestive of FMH when excluding

the differential diagnoses. The differences in clinical, laboratory, management, and outcome approaches of the two cases were shown in **Table 3.**

Table 3. The variations of clinical symptoms, laboratory tests, management, and outcome of two cases with FMH

Characteristics	Case 1	Case 2
Obstetric history	Occasionally decreased movements of fetus 1 month before delivery	Ultrasonography: fetal ascites before admission
Method of delivery	Via vaginal	Urgent ceasarean section due to decreased heart rate
At birth	Pale appearance and severe hypoxemia. No Apgar scores wasnoted.	Remarkable anemia and respiratory depression (Apgar scores of 2,3, and 5 at 1,5, and 10 minutes, respectively)
At Neonatal intensive care	Circulatory failure	Severe congestive heart failure, hydrops fetalis
Laboratory tests	Uncompensated metabolic acidosis, pH 7.03, up to 7.3 at 11h of age. Hematocrirt 15% and unmeasurable hemoglobin level	Persistent metabolic acidosis pH<6.9, Hb concentration: 2.6 g/L, high reticulocytes, negative-coomb test, normal G6PD activity range, and the absence of intraventricular hemorrhage on the cranial ultrasound
Management	Intravascular fluid therapy, umbilical catheters, red blood cells transfusion, exchange blood transfusion, and cooling therapy	Cooling therapy, red blood cells transfusion, High-Frequency OscillatoryVentilation, three inotropes, and exchange blood transfusion
KB test on the mother's blood	1.8% fetal red cells	8.3% fetal red cells
Outcome	Discharged on 13th day of life with normal nervous functions	Discharged on 10th day of life with hypertonic condition

Both obstetric histories had been uncomplicated until several days before delivery. The mother in **Case 1** was noted with decreased fetal movements and abnormal digestive

symptoms, which have been hypothesized as a transfusion reaction. In comparison to **Case 2**, the symptoms occurred more serious and sudden with acute fetal distress requiring the C-section instead of spontaneous vagina delivery. The more severe condition of **Case 2** was likely unconventional, arising from the acute fetomaternal hemorrhage on the chronic fetal anemia in the utero. Two infants immediately had tsymptoms of hypovolemic shock with severe metabolic acidosis resulting from the lack of red blood cells. There is the same pattern in the initial resuscitation and diagnosis in the two cases but there are differences in the next periods between the two. We proposed that the volume of FMH in the first case which was much less than that in the second case and prompt exchange blood transfusion in the first case could be the underlying reason for these differences. Apparently, hypoxic brain injury was avoided in the first case when the child was discharged with normal nervous functions. It was undeniable that the initial manifestations of the second infant were more adverse than the first one. Nevertheless, it was really necessary to have long-term follow-up examinations of the nervous developmental outcome. We may suggest that the small volume of blood loss via the placenta and the rapid response of resuscitation management could be as favorable prognostic factors in FMH.

IV. CONCLUSION

Severe FMH is rare but leads to severe complications, generally affects pregnancies in the third trimester. The diagnosis of FMH should be considered when there is an unexplained stillbirth or delivery of a severely anemic infant with or without hypovolemic shock. KB test is the diagnostic standard but it has some limitations. However, the KB test should be recommended to be used more widely to diagnose FHM promptly in the context of expensive and unavailable Flow cytometry tests. The prompt diagnose and treatment are necessary to save the patient's life and prevent unexpected complications.

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